REMARKS

Claims 1-48 are pending in the application. Claims 4, 5, 7, 10-12, 17-20, and 22 have been amended. New claims 25-48 have been added. Support for the amendments and new claims can be found in the original claims and in the specification at, e.g., page 2, line 14, to page 3, line 18; and page 14, line 27, to page 18, line 13. No new matter has been added.

35 U.S.C. § 102(e)

At pages 2-3 of the Office Action, claims 1-24 were rejected under 35 U.S.C. § 102(e) as anticipated by Sah et al., U.S. Patent No. 7,442,370.

Enclosed with this response is a declaration by the inventors stating that the subject matter of claims 1-24 of the present application was invented solely by them and that, to the extent that U.S. Patent No. 7,442,370 discloses but does not claim the subject matter of any of these claims, the prior application does not constitute invention "by another." Applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. § 103(a)

At pages 3-5 of the Office Action, claims 1-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Shelton et al., U.S. Patent Publication No. 20040242472 ("Shelton") in view of Milbrandt et al., U.S. Patent No. 6,284,540 ("Milbrandt"), Johansen et al., U.S. Patent No. 6,593,133 ("Johansen"), and Masure et al., U.S. Patent No. 7,067,473 ("Masure").

Applicants respectfully traverse the rejection in view of the following remarks.

Independent claim 1 is directed to a dimer comprising a first neublastin polypeptide and a second neublastin polypeptide, wherein: (a) at least one of the polypeptides is glycosylated; (b) at least one of the polypeptides is conjugated at its N-terminus to a water-soluble synthetic polymer; and (c) neither of the polypeptides is conjugated to a water-soluble synthetic polymer at a position other than the N-terminus.

As detailed in the present application, the inventors have found that when a neublastin protein is both amino terminal-conjugated to polyethylene glycol (PEG) and internally

glycosylated, serum half-life and *in vivo* potency are significantly enhanced. In particular, the inventors found N-terminal PEGylation of glycosylated neublastin to result in enhanced serum levels (following subcutaneous administration to an animal) as compared to both PEGylated/non-glycosylated neublastin as well as non-PEGylated/glycosylated neublastin (see Example 3 at pages 25-26 of the specification). The inventors surprisingly found that it is the combination of N-terminal PEGylation and glycosylation that results in significantly enhanced neublastin bioavailability. The application contains comparative data demonstrating that the significantly improved properties are associated with the claimed composition as compared to PEGylated/non-glycosylated neublastin and non-PEGylated/glycosylated neublastin.

Nothing in the cited references, considered individually or in combination, would have suggested the desirability of preparing a neublastin polypeptide that is both glycosylated and amino terminal-PEGylated or that the combination of both glycosylation and amino-terminal PEGylation would result in significantly enhanced neublastin bioavailability.

Shelton describes methods of using artemin in the treatment of nerve cell injury. Shelton contains a single, generic reference to polyethylene glycol attachment to artemin, stating that "[a]nother type of covalent modification of artemin comprises linking the artemin polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes…" Shelton at paragraph [0204]. In addition, Shelton states that artemin can be prepared in either a glycosylated or non-glycosylated form, stating that "[s]ometimes the artemin may not be glycosylated at all, as in the case where it is produced in prokaryotes…" Shelton at paragraph [0054]. Shelton does not describe or suggest polymer attachment to a neublastin polypeptide such that the polypeptide is glycosylated, conjugated at its N-terminus to a polymer, and/or is not conjugated to a polymer at a position other than the N-terminus (all three of which are required by the claims of the present application). Nothing in the general teachings of Shelton would have directed the person of ordinary skill in the art to the particular neublastin modifications that the inventors of the present application have found to result in enhanced bioavailability.

Milbrandt describes the amino acid sequence and biological activity of the artemin protein. Similar to Shelton, Milbrandt contains a single, generic reference to polyethylene glycol attachment, stating that "artemin can be stably linked to a polymer such as polyethylene glycol..." Milbrandt at column 25, lines 53-54. Furthermore, with respect to glycosylation, Milbrandt merely identifies artemin as having putative N-linked glycosylation sites. See Milbrandt at Fig. 12. Milbrandt's general statements about polymer attachment and potential native glycosylation sites of neublastin do not cure the deficiencies of Shelton or suggest the desirability of attaching a polymer to the N-terminus of a glycosylated neublastin polypeptide.

Johansen describes the neublastin protein and glycosylation of the protein. Johansen does not have any disclosure related to polymer attachment to a neublastin polypeptide. As such, Johansen does not cure the deficiencies of Shelton and Milbrandt (e.g., the failure of Shelton and Milbrandt to suggest attaching a polymer to the N-terminus of a neublastin polypeptide).

Masure describes the primary structure and biological activity of the enovin protein. Masure does not have any disclosure related to polymer attachment to a neublastin polypeptide. As such, Masure does not cure the deficiencies of Shelton, Milbrandt, and Johansen (e.g., the failure of Shelton, Milbrandt, and Johansen to suggest attaching a polymer to the N-terminus of a neublastin polypeptide).

The cited references would not have led the person of ordinary skill in the art to attach a polymer to a neublastin polypeptide in the manner that is required by independent claim 1 (i.e., wherein a neublastin polypeptide is glycosylated, conjugated at its N-terminus to a polymer, and is not conjugated to a polymer at a position other than the N-terminus). Furthermore, the cited references give no hint that improved properties would be associated with the combination of glycosylation and N-terminal PEGylation of a neublastin protein. In view of these deficiencies, the combination of Shelton, Milbrandt, Johansen, and Masure fail to render obvious the compositions and methods of claims 1-24 as well as newly added claims 25-48. Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-0035US1.

Respectfully submitted,

Date: June 22, 2011

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Customer Number 26211
Fish & Richardson P.C.
Telephone: (212) 765-5070
Facsimile: (877) 769-7945

30617971.doc